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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,020	12/31/2001	Yuehua Li	5051-451IP	8515

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,020	LI ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-89,91-93,101-105,107-109,111,112 and 116-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-89,91-93,101-105,107-109,111,112 and 116-135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 116-121 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Instant claims 116-121 depend from either claim 85 or 91. Claims 116-121 recite one of the following ranges: *at least* 15 contiguous amino acids, *at least* 20 contiguous amino acids, or *at least* 25 contiguous amino acids. These ranges lack sufficient antecedent basis, since these ranges have no upper limit, and therefore are broader in scope than independent claims 85 and 91. Claims 85 and 91 are limited to peptides *consisting* of an amino acid sequence of from 10 to 50 contiguous amino acids.

4. Claims 85-89, 101-105 remain rejected, new claims 116, 118, 120, and 122-135 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting mucus secretion *in vitro,* and for decreasing mucus hyper-secretion *in vivo* via airway administration of the MANS-peptide or active fragments thereof comprising at least the first 10 amino acids of the MANS-peptide in a mouse model of asthma, does not reasonably provide enablement for the *in vivo* therapeutic treatment of bronchitis, cystic fibrosis, chronic obstructive pulmonary disease

comprising administration of the compounds of the instant invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record.

5. Applicant's arguments filed 12-28-06 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that in light of the Parikh and Rogers declarations submitted with the response filed 12-28-06, Applicants submit that the *in vivo* mouse model of asthma provides reliable data to study the inhibition and reduction in mucus hyper-secretion as a clinical symptom in a number of respiratory diseases. Moreover, Applicants argue "they have provided evidence by *in vitro* and *in vivo* data in accepted models to study the effect of compounds/compositions on the treatment of the clinical symptom of mucus hyper-secretion in subjects. " Therefore, in view of all of the arguments, previous responses, and the previous and newly submitted declarations of Dr. Rogers, and Parikh, "applicants submit that they have provided evidence that showing reduction in the clinical symptom of mucus hyper-secretion associated with pulmonary diseases characterized by mucus hyper-secretion, it is respectfully requested that the Examiner withdraw the lack of enablement rejection of all the pending claims."

Contrary to Applicant's assertions, Applicant's own specification at page 8, teaches that there are a variety of underlying factors that may potentially influence the quantity of mucus secretion in an organism. Page 8 discloses:

> Alterations in the quantity of mucus secretions may be due to various underlying factors, including a change in the amount of mucous glycoproteins secreted from mucus-secreting cells, a change in the total number of mucus-secreting cells, or combinations thereof. Mediators released by the inflammatory response are known to act as mucus secretagogues, including lipid mediators, oxygen metabolites, and other cell-specific products. Larivee et al., In: Airway Secretion, Takishima and Shimura (Eds.), Marcel Dekker Inc., 1994, pages 469-511.

Moreover, Applicant's own specification states that determining the most effective amount of a particular peptide *"will vary depending upon the peptide, route of administration, and* ***condition being treated****,* " see page 10 which discloses:

> A "mucus inhibitory" or "mucus inhibiting" amount of a compound is that amount which reduces or inhibits mucus secretion, compared to that which would occur in the absence of the compound. A "mucus enhancing" amount of compound is that amount which enhances or increases mucus secretion, compared to that which would occur in the absence of the compound. For example, as described herein, peptides of SEQ ID NO:2 were found to increase mucus secretion in airway epithelium *in vivo* when provided in a certain amount, and to inhibit mucus secretion when provided in greater amounts. The most effective amount of a particular peptide will vary depending upon the peptide, route of administration, and condition being treated. As used herein, the term "compound" is to be broadly construed to include proteins, peptide fragments, nucleotides, oligonucleotides, and other non-protein chemicals.

Moreover, the above passage indicates that the effect of a MARCKS peptide fragment may vary depending upon its concentration. As stated above, the ability of a peptide fragment to function as a mucus enhancing or inhibiting agent varies depending upon its concentration. Applicant's own specification as filed, suggests that there is a significant level of unpredictability associated with regulating mucus secretion, as there are a variety of factors that are associated with the regulation of mucus secretion, and there is

variations in response to peptide treatment depending on the condition that is treated. Therefore, based upon the specification as filed, there is no clear correlation between the inhibition or reduction of mucus secretion in a model of asthma by means of administration of the MANS peptide, and the inhibition or reduction of mucus hyper-secretion associated with any and all respiratory or pulmonary diseases.

6. In regards to the Declarations filed under 1.132 by Dr. Parikh and Dr. Rogers submitted on 12/28/2006, it is respectfully noted that both Declarations are opinion declarations. Both the Parikh and Rogers declarations assert that the mouse model of asthma used to provide the post-filing data set forth in the Rule 1.132 Declaration filed 9-06-2005, is predictive of the efficacy of the **MANS peptide and N-terminal myristoylated peptide fragments thereof** in "the reduction of mucus hyper-secretion in a wider scope of diseases in which mucus hyper-secretion is a dominant clinical symptom." As stated above, the specification as originally filed clearly states that there are a variety of underlying factors that my influence alterations in the quantity of mucus secretion, including a variety of vaguely defined mucus secretagogues, wherein the activity of these secretagogues may be cell-specific. Moreover, the specification as filed, clearly suggests that the ability to use a peptide in a mucus inhibitory manner is unpredictable, and must be empirically determined with respect to the particular disease to be treated. In other words, although applicants may have demonstrated the efficacy of the MANS peptide and of the N-myristoylated fragments thereof in a mouse model of asthma, there is no direct correlation between these results and the production of a

mucus inhibitory benefit produced in any disease wherein mucus hyper-secretion is the dominant clinical finding.

7. Furthermore, both the Rogers and Parikh Declarations are not commensurate in scope with the claimed invention. Instant claims 85-89, 91-93, 111-102, 116, 118, 120, 122-123, 126, 128, 130, 132, and 134 are not limited to the use of **MANS peptide and N-terminal myristoylated peptide fragments thereof**, the scope of these claims includes the administration of peptides up to 50 amino acids in length for the reduction of mucus hyper-secretion in any animal. However, the scope of the Parikh Declaration (see paragraphs #2 and #5), and the Rogers Declaration (see paragraph #3, and #4) addresses only the administration of the MANS peptide and its N-terminal myristoylated fragments thereof.

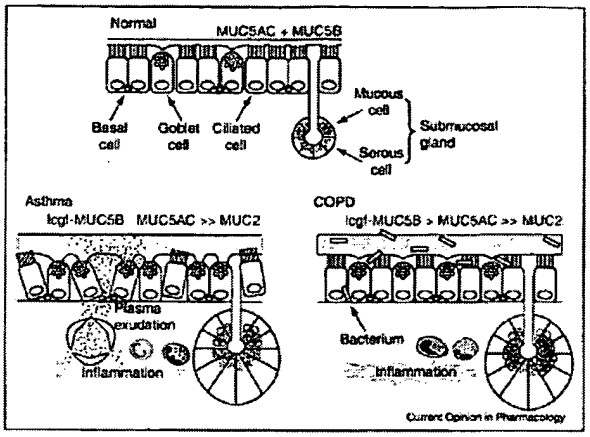
8. The Rogers Declaration, (at paragraph #4) traverses the Examiner's question regarding the reliance on post filing references (as set forth in the prior Office Action) to support the enablement of the present invention. According to Dr. Rogers, the Li et al. (2001) publication represents a peer reviewed publication wherein Li et al. "shows similar experiments to study the effect of MANS peptide on mucus hyper-secretion in NHBE cells." The examiner agrees with Dr. Rogers on this point in regards to the disclosure of Li et al. However, in regards to the other references provided in Attachment C to the Rogers Declaration of 6/07/2006, their disclosures appear to contradict the above statements by Applicants, particularly that administration of the MANS peptide and its N-myristoylated fragments would be therapeutically effective to treat any disease wherein mucus hyper-secretion may be the dominant clinical

symptom. For example, according to Rogers et al. (2006; Attachment C, Exhibit 8 of the Rogers Declaration submitted 6/07/2006), there are significant differences between the pathophysiology of the airway mucus hypersecretory phenotype in asthma, COPD, and cystic fibrosis (see Figure 2), moreover there are multiple factors that function in mucus exocytosis see Table II, page 121. Rogers (2006) clearly sets forth the differences in pathophysiology relating to mucus hyper-secretion between asthma, COPD and cystic fibrosis see the following passage from page 120 of this reference:

> Different MUC gene products may be present in respiratory secretions in asthma and COPD. MUC5AC and a low-charge glycoform of MUC5B are the major mucin species in airway secretions from patients with asthma, COPD and CF (42–46). There is significantly more of the low-charge glycoform of MUC5B in the respiratory diseases than in normal control secretions (46). Interestingly, there is a proportional increase in the MUC5B mucin over the MUC5AC mucin in airway secretions from patients with COPD or CF, compared with secretions from patients with asthma (42). The significance of the change in MUC5B glycoforms to bacterial colonization between the different diseases is unclear. However, it is interesting that it is observed in COPD and CF, where patients are prone to bacterial chest infections (4,23), rather than in asthma where patients are not notably prone to infection.
>
> In contrast to normal airways, there is upregulation of MUC5AC in the airway epithelium of patients with COPD compared with smoking (and non-smoking) controls (27). Goblet cells in the airways from patients with COPD contain not only MUC5AC but also MUC5B (44,47) and MUC2 (7,48). The latter distribution is different to that in the airways of patients with asthma or CF, where MUC5AC and MUC5B show a similar localization to that in normal subjects (49,50). It is noteworthy that although MUC2 is located in goblet cells in irritated airways, and MUC2 mRNA is found in the airways of smokers (26), MUC2 mucin is either not found in airway secretions from normal subjects or patients with chronic bronchitis (43), or is found only in very small amounts in asthma, COPD and CF (46,51). The significance of the above combined observations is unclear, but suggests that there are differences in goblet cell phenotype between asthma and COPD.

Moreover, Rogers (2004; Attachment C, Exhibit 5 of the Rogers Declaration submitted 6/07/2006), diagrams the differences between the mucus pathophysiology of asthma and COPD, see page 243:

Figure 2



Mucus pathophysiology in asthma and COPD: similarities and differences. In asthmatics, there is increased luminal mucus, a similar or increased ratio of mucin (MUC) 5B (low charge glycoform [lcgf]) to MUC5AC, small amounts of MUC2, epithelial 'fragility', marked goblet cell hyperplasia, submucosal gland hypertrophy (with normal mucous to serous cell ratio), 'tethering' of mucus to goblet cells, and plasma exudation. Airway inflammation involves T lymphocytes and eosinophils. In COPD, there is increased luminal mucus, an increased ratio of lcgf MUC5B to MUC5AC, small amounts of MUC2, goblet cell hyperplasia, submucosal gland hypertrophy (with an increased proportion of mucous to serous cells), and respiratory infection (possibly owing to reduced bacterial enzymatic 'shield' from reduced serous cell number). Pulmonary inflammation involves macrophages and neutrophils. Many of these differences require data from greater numbers of patients.

Therefore, contrary to Applicant's assertions, and the assertions made in the Parikh and Rogers Declarations filed 12/28/06, there is clear no nexus between the reduction of mucus hyper-secretion in a mouse model of asthma by administration of the MANS peptide and its N-myristoylated fragments, and the reduction of mucus hyper-secretion in other disease states that are pathophysiologically distinct from asthma.

As stated in the prior Office Action, there is no evidence of record that demonstrates that the MANS peptide (*and its N-myristoylated fragments*) would function to modulate all inflammatory mediators associated with the full scope of diseases encompassed by the instant claims. The lack of any working in vivo examples in the specification as filed is exacerbated because the invention is in a highly unpredictable art-regulating the airway mucus hyper-secretion-and while the level of skill of a practitioner in the art may be high, the state of the art at the time of the instant invention

was in fact unknown and untested in regards to the administration of peptide fragments for the treatment of any disease wherein mucus hyper-secretion is the dominant clinical symptom.

Double Patenting

9. Claims 85-89, 91-93, and 101-105, 107-109, 111-112 remain provisionally rejected, and new claims 116-129 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 52-54, 57-67, 70-75 and 85-91 of copending Application No. **10/802,644**. Although the instant rejection is a provisional rejection, and can be withdrawn if it is the only remaining rejection of record, (See MPEP § 804, see page 14 of Applicant's reply filed 12/28/2006), the instant rejection is maintained since there are other remaining rejections set forth above.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford whose telephone number is 571-272-0757. The examiner can normally be reached on M-F, 10:00 AM through 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Janet L. Epps-Ford, Ph.D.
Primary Examiner
Art Unit 1633

JLE